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THE LUNGS IN ANAPHYLAXIS AND IN CONDITIONS SIMULATING ANAPHYLAXIS.

BY HOWARD T. KARSNER, M.D.

(From the State Serotherapeutic Institute, Vienna, Prof. Dr. R. Kraus, Director, and from the Laboratory of Pathology, University of Pennsylvania, Philadelphia, Pa.)

THE purpose of this paper is to aid in the identification of anaphylaxis as a distinct biological entity. Since the early work on true anaphylaxis by Richet, Arthus, von Pirquet, Otto, Rosenau and Anderson, and others, various attempts have been made to produce by a single injection of some substance the same effect

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that is produced by the repeated injection, with suitable time intervals, of a protein, particularly an animal protein. Of the substances used in the attempts to produce an artificial anaphylaxis in guinea-pigs, fresh ox serum (toxic for guinea-pigs), Witte's peptone, and various hematoxic substances such as ricin, abrin, solanin hydrochlorate, hirudin, sodium oleate, and some others have been employed. Symptomatically and to a certain extent physiologically, the effects of the administration of these substances resemble those of true anaphylaxis. There is much question, however, as to whether or not the similarity is so close biologically; and it was with the idea of throwing some light on the differences between true anaphylaxis and these conditions which in many ways simulate it that the present anatomical study was undertaken.

The pathological anatomy of anaphylaxis was first studied by Gay and Southard,[1] who declared the lesions to be: Vascular dilatation and hemorrhages, both gross and minute, especially in the abdominal viscera; fatty degeneration in voluntary muscle fiber, heart muscle fiber, and nerve fiber. Rosenau and Anderson[2] ascribe the vascular dilatation to shock as a general condition, not necessarily anaphylactic, and state that the "macroscopic congestions and hemorrhages were frequently absent in guinea-pigs poisoned by a second injection of horse serum given into the brain." They were "unable to confirm Gay and Southard's findings in regard to the fatty changes." Auer and Lewis[3] have pointed out what they consider "the most characteristic sign of immediate anaphylaxis in the guinea-pig." They describe the lungs as being distended so as to apply themselves closely to the chest wall. The organ is pallid or bluish, light in weight, buoyant in water, and of spongy consistence. Occasionally fine points of hemorrhage are seen. The trachea and bronchi are dry, but often show a marked congestion of the mucosa. Observations of Kraus confirm this, and my own studies further support it. The slight exception I find is that the hemorrhages are very infrequent and that the reddening of the trachea and bronchi is by no means constant.

My studies have been made with guinea-pigs weighing about 250 grams. The second injections of horse serum and the primary and only injections of other substances were made into the jugular vein. The histological preparations in all cases were made from tissues fixed in Zenker's fluid and stained with hematoxylin and eosin and with the Mallory connective-tissue stain.

In order to make clear the entire series of experiments an outline is appended.

[1] Journal of Medical Research, 1907, xvi, 143.
[2] Archives of Internal Medicine, June, 1909, iii.
[3] Journal of Experimental Medicine, 1910, xii, No. 2.

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I. Experiments with anaphylactic guinea-pigs (horse serum).
II. Experiments with peptone injections.
III. Experiments with toxic serum (ox serum).
IV. Experiments with immune serum.
    1. Hemolytic amboceptor.
    2. Precipitating amboceptor.
V. Experiments with hemotoxic agents:
    1. Ricin.
    2. Abrin.
    3. Solanin hydrochlorate.
    4. Sodium oleate.

I. In the work with the anaphylactic guinea-pigs sensitization was accomplished by the subcutaneous injection of 0.05 c.c. normal horse serum. Secondary fatal doses of 0.5 c.c., 1 c.c., 1.5 c.c., 3 c.c., were given in the jugular vein. Rapid death ensued with the usual symptoms of anaphylaxis, *i. e.*, more or less general convulsive movement, cyanosis, respiratory effort, and final cessation of respiration with the heart still beating. Autopsy showed the heart to be slightly or not at all dilated and when opened free from clots. The lungs grossly in all cases were markedly distended, pallid, light in weight, spongy in consistence, but in no instance showed any gross hemorrhage or well-marked congestion of the bronchi. Histologically, the bronchi were found to be constricted in all the lungs and showed marked folding of the mucosa. The arteries also showed well-marked constriction. The large veins were slightly distended and showed the presence in some instances of masses of conglutinated blood corpuscles. In one pig there was found well-marked fading of the red corpuscles. In some of the capillaries that were not emptied by the marked alveolar distention an occasional occluding mass of conglutinated corpuscles was found, but this was by no means a frequent occurrence. A noticeable feature was the presence of a moderately marked perivascular edema occupying both the perivascular lymph spaces and the loose connective tissue in their neighborhood. The edematous fluid showed small amounts of fibrin with the Mallory connective-tissue stain. The alveoli were distended and showed frequent rupture into one another; the walls were markedly thinned and the alveolar spaces empty, except in the case of the pig which received 3 c.c. horse serum. In one section from this pig a small area showed filling of the alveoli with red blood corpuscles—an area of microscopic hemorrhage. In so far as the alveoli were considered, the lungs showed the typical picture of vesicular emphysema.

II. Several guinea-pigs were given injections of Witte's peptone, 10 per cent. in 0.85 per cent. sodium chloride solution. The doses were 3 c.c. and 3.5 c.c. of this solution. The symptoms were

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typical of anaphylaxis. The autopsies showed well-marked distention of the lungs, a condition very closely resembling that of the true anaphylactic lungs except that small macroscopic hemorrhages were more frequently observed. The heart was slightly dilated and free from clots. Histologically the picture simulated that of anaphylaxis very closely with the exception that the bronchial and arterial constriction were not so marked. The perivascular edema was about the same and the same degree of conglutination of red blood corpuscles in both capillaries and veins was observed. No microscopic hemorrhages could be found, so it is believed that the areas which grossly were supposed to represent hemorrhage corresponded to small foci of relative atelectasis observed microscopically, in which the capillaries were much distended with blood.

III. Three guinea-pigs were injected respectively with 0.5 c.c., 1 c.c., and 2 c.c. fresh ox serum. Death ensued very rapidly with symptoms like those of anaphylaxis. The autopsies showed small, intensely congested lungs with frequent punctate areas of hemorrhage and a markedly dilated heart which contained small clots of blood. The cardiac dilatation affected the right side more than the left. Histologically, the lungs showed moderate constriction of the bronchi, but the arteries were practically normal in caliber. The veins, however, were markedly distended and showed fairly large masses and meshes of fibrin. Perivascular edema was present in about the same degree as in the anaphylactic lungs. The alveoli in some places were markedly distended and ruptured, but for the most part were of normal size or collapsed, showed thick congested walls and well-marked capillary occlusion with hyaline conglutinated red blood corpuscles. The alveolar spaces in many places showed marked edema and hemorrhage.

IV. Two types of amboceptor were used in the experiment, the first the serum of a rabbit immunized against sheep's corpuscles so that the serum in a dilution of 1 to 2400 dissolved 1 c.c., 5 per cent. corpuscle suspension, the second a precipitin obtained by immunizing a rabbit against horse serum, the resulting serum producing a precipitate when acting on horse serum of a dilution of 1 to 1,000,000. The intravenous injection of 5 c.c. of such a precipitating serum produced only slight respiratory disturbance in the guinea-pig followed by complete recovery. The intravenous injection of 0.5 c.c., 1 c.c., 2 c.c., 3 c.c. of the hemolytic amboceptor (1 to 2400) was fatal, with symptoms closely simulating true anaphylaxis. Hemolytic amboceptor of less strength (1 to 800) produced no more effect than normal rabbit serum. Of the guinea-pigs injected with the stronger hemolysin, all died with symptoms of anaphylaxis. At autopsy, the lungs were found to be moderately distended and showed intense congestion, pinpoint hemorrhages, and easily demonstrable edema. The heart

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was dilated and filled with dense black clot. Histologically, the bronchi and arteries showed very moderate constriction. The veins were considerably distended and filled with red blood corpuscles, hyaline masses of serum, fibrin threads, and in some instances showed conglutination of the corpuscles. The perivascular spaces were markedly edematous, and in many places showed extensive hemorrhage with fibrin formation. The alveoli showed well-marked distention and rupture of their walls. The walls showed moderate congestion and conglutination of the corpuscles. The alveolar spaces in some few places showed hemorrhage, but the most noticeable feature of these slides was the extensive edema present in the alveoli.

V. Of the hematoxic agents used, the effects of ricin and abrin were so closely alike that a combined description seems justified. The ricin was given in doses of 0.001, 0.002, 0.003, 0.01, 0.02 gram, the abrin in doses of 0.001, 0.004, 0.01, 0.02 gram. The pigs died in all cases at periods varying from ten to twenty-four hours. Grossly the lungs were moderately distended, occasionally showing small areas of atelectasis. The organs were deeply congested and showed numerous points of hemorrhage. The pleura in several of the animals showed a moderate amount of clear, limpid yellow fluid. The heart was dilated and filled with dark red clot. Histologically the lungs showed moderate constriction of bronchi and arteries and marked distention of veins and many of the capillaries. All the vessels showed conglutination of the corpuscles which in the capillaries appeared to have caused occlusion. Well-marked perivascular edema was present. The alveoli showed moderate distention, edema, and in some places hemorrhage.

Solanin hydrochlorate was given in doses of 0.002, 0.004, and 0.005 gram. Death was rapid with sypmtoms of anaphylaxis. At autopsy the lungs were found to be slightly distended, and in one case distinctly collapsed, with a few areas of distention. Slight pulmonary congestion was present. The heart was still beating and showed the presence of fine clots. Histologically there was moderate constriction of arteries and bronchi; the veins were distended with red blood corpuscles, hyaline serum, fibrin, and showed moderate conglutination; the capillaries also showed occluding masses of conglutinated corpuscles. The perivascular spaces showed moderate edema, sometimes richly fibrinous. The alveoli showed fairly well marked distention alternating with areas of collapse. Slight edema and less noticeable hemorrhage were seen in the alveolar spaces.

Sodium oleate was used in doses of 0.05, 0.1, and 0.2 gram. Death ensued very quickly with symptoms of anaphylaxis. The lungs showed distention, marked congestion, numerous hemorrhagic points, and distinct edema. The heart was markedly dilated and filled with clots. Histologically the lungs showed

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distinct but not very marked constriction of the bronchi and arteries and well-marked distention of veins and capillaries. There was very marked conglutination of corpuscles in the larger veins and in the capillaries. The perivascular spaces were moderately edematous. The alveoli showed considerable distention and slight rupture of the walls. The alveolar spaces were markedly edematous, almost as much as in the lungs after hemolytic amboceptor injections, and in several places hemorrhage had occurred into the alveoli.

The similarity between the lung, heart, and blood conditions after the injection of abrin, ricin, and sodium oleate, and after the injection of fresh (toxic) ox serum is very close, and suggests that the action of ox serum is of a nature similar to the action of these hemotoxic agents.

As a result of these studies it seems fair to conclude:

1. That the lung picture in the horse serum anaphylaxis of guinea-pigs is quite distinctive, the most noticeable features being bronchial constriction and marked distention and rupture of alveoli.

2. That the pictures presented by the various agents suggested to produce artificial anaphylaxis are quite different from those of true anaphylaxis except in the case of peptone injections, where the similarity is so close that only non-essentials serve to distinguish it.

3. The effect on the lungs of hemolytic amboceptor is characterized, especially by marked edema; that of toxic ox serum by hemorrhage; and that of the hemotoxic agents mentioned is closely similar to that of fresh ox serum.

4. Conglutination (fusion) of erythrocytes is common to all the processes studied, but is more marked in the non-anaphylactic than in the truly anaphylactic conditions.

In conclusion, I wish to thank Prof. Dr. R. Kraus at whose suggestion this study was undertaken, for facilities used in the earlier parts of the work.

Discussion.

Dr. R. M. Pearce: The very interesting paper of Dr. Karsner presents two points for discussion. The first is in connection with the negative results which were obtained by the injection of serum characterized as a "precipitating" serum. One of the theories concerning anaphylaxis which has recently attracted considerable attention is that which assumes that the phenomena resulting from the injection of a toxic dose are due to the precipitation of proteins within the cell. I do not now recollect which system Dr. Karsner used in preparing his precipitin, but if it was

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directed against the protein elements of the guinea-pig, his observations would detract from the importance of the theory which assumes that the reaction of anaphylaxis depends upon the precipitation of such protein elements.

The other point is in regard to the results obtained with the injection of peptone as contrasted with the true anaphylactic reaction. Both of these phenomena are characterized by a sudden drop in blood pressure. This may be seen best, perhaps, in the dog, as has been shown by Eisenbrey and myself, but is more or less characteristic of the reaction in the rabbit and guinea-pig as well. This sudden drop of blood pressure in the dog, essentially a condition of shock, is perhaps the equivalent of the respiratory disturbances in the guinea-pig. It is of great interest in this connection to note that Auer and Lewis refer the latter to the effect on the smooth muscle of the bronchioles. In the dog, Eisenbrey and myself believe the action to be on the smooth muscle of the bloodvessels of the peripheral circulation, especially in the splanchnic area. The reactions differ, it is true, in that the effect on the bronchial muscles is a contraction, while in the dog the vessel muscle is paralyzed, but this selective action in either instance indicates that the anaphylactic reaction is in some way associated with an effect on the function of smooth muscle or of the nerves controlling such nerves. Detailed observations carried out in the thorough manner which characterizes Dr. Karsner's work, must be continued in the hope of eventually reaching a solution of this most interesting biological phenomenon.

December 22, 1910.

SPECIMENS PRESENTED JANUARY 12, 1911.

DR. SIDNEY J. REPPLIER:

Specimen Showing the Simultaneous Occurrence of Carcinoma and Sarcoma of the Breast.

M. W., white, female, aged sixty-four years, operated on by Dr. Wm. L. Rodman at the Presbyterian Hospital. No history of injury obtainable. Tumor had been present for three or four years but had begun to grow rapidly in the last few months. On palpation several rounded masses could be felt, one of which seemed cystic and was discolored a reddish brown.

Pathological examination shows the breast to be almost entirely composed of new growth. The area under the discolored spot is a cyst the size of a hen's egg containing a dark red fluid. The tumor mass appears to be made up of distinct lobules differing in gross

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appearance. Some of these areas show microscopically as a spindle-cell sarcoma. Others gave somewhat the appearance of an adenocarcinoma. In order to settle the matter, the tumor and slides were referred to the Committee on Morbid Growths.

The Committe on Morbid Growths submits the following report on the tumor of the breast referred to it by Dr. Sydney J. Repplier:

Grossly the tumor is a massive cystic growth invading the greater part of the breast and showing no limitation of its extension either in the form of a capsule or the compression of the surrounding breast tissues. The cysts are of variable size, the largest being 4 cm. in diameter. The lining of the cyst wall is generally smooth and regular and the content a dark brown, homogeneous, translucent, semi-solid mass.

Numerous sections from fifteen blocks of tissue were made and the presence of a spindle-cell sarcoma determined with ease and certainty, the greater part of the tumor evidently being of this nature. In places mucoid degeneration has occurred in the sarcomatous tissue, but this is a feature exceptional rather than general. The tissue arrangement is such as to lead the Committee to think that the tumor probably is periductal in origin, but this opinion is not final, and certainly is not of great importance in the report.

Several sections, more especially those taken from the neighborhood of the large cyst, show well-marked epithelial proliferation quite independent of the sarcomatous condition, and were these sections examined alone there would be no suspicion of the presence of sarcoma in other parts of the same organ. The gland spaces are markedly irregular in shape and size, and the cells show "piling up" within the lumina of the glands. In addition, numerous areas show distinct penetration of the basement membrane, with the formation of cords and smaller masses of epithelial cells lying apparently free in the tissue. As has been mentioned, these areas show no direct association with the sarcoma, and the opinion of the Committee is that this very evident adenocarcinoma is an independent growth.

Several sections of an enlarged axillary lymph node show well-marked endothelial hyperplasia, but no invasion by either sarcoma or carcinoma.

In none of the sections could cartilage, bone, nerve, or other tissue be demonstrated which would serve to place the tumor in the class with what commonly are called mixed or teratoid tumors.

The committee is of the opinion that the breast shows the simultaneous presence of spindle-cell sarcoma and adenocarcinoma.

HOWARD T. KARSNER.
JOHN SPEESE.
BORDEN S. VEEDER.

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OF MICHIGAN

DR. ALFRED STENGEL AND DR. O. GARRISON MARKS:

A Report of Six Cases of Trichinosis, with One Death, Treated at the Pennsylvania Hospital during the Services of Drs. Stengel and Tyson, and in the months of November and December, 1910.

All the patients were Italian, and all from the southern part of the city, except one, who was from Bridgeton, N. J.

Case 1 is especially interesting on account of the close resemblance of the beginning of the disease to typhoid fever.

Patient was admitted November 11, giving a history of having been sick seven days, starting off with general malaise, slight abdominal pain and diarrhea, rather severe headache, loss of appetite, and feeling feverish and chilly, but no distinct chill. Temperature on admission, 102.2°.

Physical examination. Negative, with exception of an enlarged and distinctly palpable spleen. There was also present over abdomen and back a rash typical of the rose-colored spots seen in typhoid fever.

Blood on admission: Leukocytes, 16,000; Widal negative. Four days later (eleventh day of disease) temperature came gradually down to 99°, intestinal symptoms and headache having subsided, and patient was comfortable.

Two days later (thirteenth day of disease) temperature within six or eight hours rose to 103.3°, eyes became swollen, face puffed, and muscles, principally flexors and biceps, were especially painful and tender and had the consistency of rubber; he was able to extend arms only to about angle of 45 degrees. Patient would lie on his side in bed, and assuming a sort of semiflexed position, relax all flexor muscles.

Blood at this time (thirteenth day of disease): Leukocytes, 18,000; and differential count showed 10.5 per cent. of esinophiles and 83 per cent. polynuclears.

On the sixteenth day of disease muscle excised from biceps showed the trichina lying between the muscle fibers, and no evidence of becoming encysted.

The highest percentage of esinophiles was 24.3 per cent., taken on the twenty-fourth day of disease.

Patient ran a temperature between 102° and 103°, with evening rises and morning remissions similar to that of typhoid fever for fourteen days, ending by lysis with the greater difference between morning and evening temperature, also seen in the lysis of typhoid fever.

As temperature came down the muscular symptoms gradually subsided, and patient made a satisfactory recovery.

Last differential just before patient was discharged showed 16 per cent. of eosinophiles.

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Cases 2, 3, and 4 were of the same family. Father, mother, and five-year-old boy. Mother was admitted on twentieth day of disease, and was in a very weakened condition, resulting from the pronounced gastro-intestinal condition. Diarrhea was profuse, losing as high as twenty stools in twenty-four hours.

Blood on admission: Leukocytes, 16,000; differential showed 6.4 per cent. eosinophiles. Patient gradually grew worse, developing a pleurisy, and the highest eosinophilia was 10.4 per cent. just a few days before death, which occurred on the thirty-seventh day of disease.

Muscle excised before death from biceps showed encysted trichina.

No muscular symptoms were present on admission.

Autopsy performed and anatomical diagnosis as follows: Trichinosis; pulmonary infarction of right lung; acute fibrinous pleurisy; acute enteritis; fatty degeneration of liver; cloudy swelling of heart and kidneys.

The father ran a course similar to Case 1, but with more pronounced symptoms. The swelling about the eyes and face more marked, and was similar in appearance to a case of acute nephritis.

On admission muscular symptoms were well marked.

Blood: Leukocytes, 31,000; differential showed eosinophilia of 53 per cent. This was about the tenth day of disease.

Muscle excised from biceps showed numbers of trichina being parallel to fibers. Few were curled up, as if beginning to become encysted.

Son was apparently well when admitted to hospital for study, although he was rather anemic looking, eyes slightly puffed, no muscular symptoms, and no temperature. Had a mild leukocytosis, 10,000, and 28 per cent. eosinophiles. No trichina were found in muscle excised from biceps.

Cases 5 and 6 were rather light attacks. Muscular pains not very marked, Eosinophiles ranging between 10 and 20 per cent. Ran a temperature for eight or ten days between 101° and 102°. A number of attempts were made to find the trichina in the blood and feces, but without success.

Dr. J. V. Cooke. In connection with this report there are one or two points of pathological interest. In the child admitted during convalescence there was an eosinophilia of 28 per cent., and yet the trichinæ could not be demonstrated in the muscles; while in the fatal case in which the eosinophiles were only 10.4 per cent. just before death numerous trichinæ were found in all the involuntary muscles; these were surrounded by very few eosinophiles. In this case the bone marrow showed many eosinophilic myelocytes. It may be that the height of the eosinophilia in trichinosis is an indication of the degree of reaction on the part of the individual. I might state further that very numerous adult female trichinæ were found in the small intestine of the fatal case.

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OF MICHIGAN

DR. WILLIAM PEPPER. I wish to refer to a case of trichiniasis seen recently at the University Hospital. The patient was a man who had suffered for several years with frequent attacks of angioneurotic edema; the localized swellings occurring in various parts of his body. On admission to the Hospital he had a normal eosinophile count, and a slight amount of swelling in one of his hands. Two or three days later he developed a considerable amount of edema around the eyes, accompanied with a high temperature and an eosinophile count of 50 per cent., but unaccompanied with any pain. He stated that in his previous attacks of angioneurotic edema he had never had fever, and that the attacks lasted for only a few hours. Notwithstanding his past history, in the light of the prolonged attack of edema which was localized around the eyes and accompanied by fever and eosinophilia, we removed a portion of muscle from the biceps and found the parasites. The occurrence of trichiniasis in a patient with chronic angioneurotic edema was an interesting and confusing coincidence.

DR. WARD BRINTON AND DR. R. C. ROSENBERGER:

Uncinaria Infestation in an East Indian.

The case was a male East Indian admitted to the service of Dr. Ward Brinton at the Philadelphia Hospital.

Blood count showed red cells from 3,540,000 to 2,450,000, and white cells, 11,600 to 10,800; the average of five differential counts of white cells showed: Polynuclears, 45.3; small lymphocytes, 17.6; large lymphocytes, 28.6; eosinophiles, 7.2; basophiles, 1.

The highest count of the eosinophiles was noted on first examination, 10.7 per cent; the highest count of large lymphocytes on the fifth, 42 per cent.

No malarial plasmodia or Leishman-Donovan bodies were demonstrable in the peripheral blood, though a few bodies were found in the blood obtained by puncture of the spleen which closely resembled plasmodia.

Thirty-three examinations of the stools made from November 6, 1910, to January 7, 1911, revealed ova of the Ascaris lumbricoides, Tricocephalus dispar, and Necator americanus.

In every stool examination except the nineteenth, twenty-first, thirty-first, and thirty-third the ovum of the Necator americanus was found.

Following the administration of thymol, about thirty or forty hookworms were expelled, the last treatment followed by the expulsion of about a dozen mutilated worms. In one stool encysted ameba were observed.

DR. ALLEN J. SMITH. This example is one of the instances going to prove that Necator americanus is, in reality, not limited in its

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distribution to America, as was supposed when the species was first named. It is recorded a number of times from India, has been found in the dwarf races of the interior of Africa, who have very little communication with other peoples, and has been described also from the chimpanzee in Africa; and doubtless originally the parasite was of African occurrence and was introduced into America by the negroes in early times.

The broken condition of the worms exhibited here I would suggest may be due to digestion after destruction by thymol. If retained after death by adherence to the mucus covering the surface of the mucous membrane in many of these patients, it is altogether probable that complete or partial digestion of the parasites might take place. At autopsies in animals it is not infrequent to find some of the intestinal parasites showing the appearance of digestion or disintegration by the intestinal bacteria or by the digestive fluids.

DR. G. W. NORRIS AND DR. A. F. JACKSON:

The Heart, Brain, and Spinal Cord from a Case of Cerebrospinal Meningitis.

Over the vertex of both right and left hemispheres of the brain there is a thick fibrinopurulent exudate, involving chiefly the pia arachnoid. A thinner exudate is present over the base. The remainder of the brain surface is reddish and injected. On placing the brain upon the table (fresh) the hemispheres separate somewhat as if the ventricles were filled with fluid.

There is a thin purulent exudate over the spinal cord (pia arachnoid), more marked on the dorsal surface of the thoracic and portions of the lumbar and cervical regions.

The mitral valves show several fresh vegetations, about 1 to 4 mm. in diameter. The largest one was cut in opening the heart.

Blood culture and spinal fluid smears showed the Gram negative meningococcus of Weichselbaum.

DR. G. W. NORRIS AND DR. G. F. LULL:

The Genito-urinary Tract from a Case of Prostatic Hypertrophy and Chronic Cystitis, with Cystic Calculus and Ascending Infection of the Ureters, Causing Pyelitis and Suppurative Nephritis.

Specimen consists of right and left kidneys, ureters, urinary bladder, and prostate gland.

The prostate gland is firm, whitish in color, and is enlarged, measuring 4.3 cm. in diameter. Upon the mucosa of the bladder behind the prostate is a roughened area 2 cm. in diameter, and

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loosely attached to this point is an irregular stone weighing 3 grams and composed of phosphates and carbonates.

The bladder wall is markedly thickened, measuring at some points 1.5 cm. The mucosa is covered with a grayish-green exudate and the cavity is filled with a thick, turbid urine.

The ureters on either side are thickened. The renal pelves are dilated and the mucosa is covered with a grayish material.

The renal capsule is thickened and is adherent, and when removed leaves a rough surface with small grayish-white dotlets here and there. The cortex of the organ is narrowed at places, it is striated, and contains numerous grayish areas.

The tissues around the kidney are markedly adherent to the capsule of the organ.

THE CELLULAR BASIS OF THE DETERMINATION OF SEX.[1]

By Thomas H. Montgomery, Jr., Ph.D.

(Abstract.)

In the present place it is intended to deal with sex determination from the standpoint of our knowledge of the germ cells, so far as a short discussion permits.

Sex is the relation of difference between individuals of the same species, some of which reproduce, while others fertilize. In the multicellular animals there are various states of sexuality. The most usual condition is where there are separated and functional males and females. But frequently both male and female are united in one bisexual individual, as in hermaphroditism; and in this case it is quite general that the individual is in succession male, hermaphrodite, and female. Hermaphroditism is probably a secondary and not a primitive condition. In rare cases, as certain of the Rotatoria, only females appear to exist, and the species lacks males entirely. Again certain females may become normally barren, as in the workers of certain bees and ants. Then in certain colonial species of Bryozoa and Cnidaria certain individuals are wholly sexless. And in the cases known as parthenogenesis, a long sequence of female individuals may be produced in the course of the year, and both males and females only in the last generation, as well illustrated in the common plant lice, this condition being a kind of alternation of generations known as heterogenesis.

Thus, the phenomenon of sexuality becomes very complex in its

[1] Published in full in International Clinics, 1911.

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entirety, and is by no means only a matter of difference between males and females. And it may also be noted that the numerical ratio of the sexes is not always 1 to 1, as generally assumed, even where there are separated males and females in the same generation. This matter is mentioned here simply to show that any theory of sex determination must also explain the sex ratio, which may differ with the species.

We come now to the inquiry of what processes determine that an egg shall develop into a male or a female individual. And just here it is to be noted that the sex of the individual is probably determined not later than the stage of fertilization of the egg, That is to say, despite the numerous experiments made in the hope of securing positive results, it has not yet been possible to alter the sex ratio by external influences acting after the one-cell stage of the organism. The nearest approach to securing this end has been reached by Shull, who found that by altering external conditions the relative members of male-producing and female-producing individuals can be changed in Rotatoria. The main result reached after much experimentation and discussion is that the sex of the individual is probably established not later than the stage of fertilization; and there is still no body of evidence that the sex state so established can be changed by influences acting during a later stage.

In this connection may be noted the interesting cases of polyembryony, where several embryos came from the same egg. This has long been known for trematodes and cestodes, more recently for some parasitic wasps (Marchal, Silvestri), and has been made known within the year by Newman and Patterson for the armadillo. In these cases all the embryos from one egg are of the same sex, which shows that the sex feature must be stamped on the organism very early.

In certain animal groups (Aphids, Dinophilus, Phylloxerans, Rotatoria, Arachnids) there are two kinds of eggs produced, larger ones that form females and smaller ones that produce males. These differences are established early in the growth period of the germinal cycle, before the maturation divisions. These two kinds of eggs may be produced by the same individual, or (Rotatoria) by different individuals. This is a very interesting phenomenon, showing a very early distinction of sex in the egg, long before fertilization, and is found in species where the adult males and females differ greatly in size. It would suggest the hypothesis that in all species there may be male and female eggs differentiated before fertilization, an idea originated by Beard and Castle, though not generally associated with any size difference. What is the process that differentiates these two kinds of eggs, we do not know. Malmsen has suggested that the female eggs of Dinophilus arise by the fusion of a number of eggs, but he has not proved it.

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Again, in parthenogenesis sex is determined without fertilization. In normal parthenogenesis, where the egg develops to the adult stage, there are found two sexual resultants: in homoparthenogenesis only one sex is produced from unfertilized eggs; this may be arrhenotoky, or the formation of males, as in the honey bee, or thelytoky, the formation of females alone, as in certain moths; in heteroparthenogenesis both sexes are produced from unfertilized eggs, as in aphids, rotatoria, and daphnids. In digenetic trematodes hermaphrodites develop from unfertilized eggs, while in other groups hermaphrodites come from fertilized eggs. In the case of the bee, ant, and hornet, males or drones are produced from unfertilized eggs that have formed two polar bodies, and consequently have the reduced number of chromosomes, a fact established by the study of the spermatogenesis of these species; but the parthenogenetic eggs of the other species mentioned give off only one polar body, consequently have the normal number of chromosomes. Thus, unfertilized eggs of bees that have the reduced number of chromosomes form males, which would agree with the older hypothesis of Minot that the polar bodies eliminate all the male substance from the egg. But the fact that unfertilized eggs with the normal number of chromosomes may give rise to either sex, or to both sexes, shows that this hypothesis is probably no adequate explanation.

The reduction division is the mitosis following the growth period of the germ cells, that separates entire chromosomes from each other, thereby reducing the number of chromosomes one-half. In the parthenogenetic eggs of aphids, which give rise to either males or females, no reduction division takes place, because there is no synapsis or conjugation of chromosomes. Consequently, in these cases sex is not determined by the mechanics of chromosome distribution. Further, sex cannot be determined by any sorting of the chromosomes in aphids and rotatoria, for here there is no reduction division and every egg has the same kinds of chromosomes.

These preceding examples show that the prospective sex of an egg may be determined before the maturation divisions, before the sperm enters. But the entrance of a sperm may alter the sex. Thus the egg of the bee when not fertilized forms a male, but when fertilized, a female. And Whitney has shown that the small egg of a rotatorian, destined to give rise to a male if not fertilized, forms a female when fertilized. This leads us to consider how sex may be altered by fertilization.

One of the most recent and most discussed matters with relation to the determination of sex is that of dimorphism of spermatozoa, where there is more than one kind in a species, and whether some of these may be male-producing and others female-producing. In prosobranch molluscs and certain moths there are two kinds of

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sperm, known best from the researches of Meves, but one of these kinds lacks chromatin to great extent or entirely (oligopyrene or apyrene sperm), and probably does not enter the egg; here then there is really only one kind of functional sperm. In another insect, Euschistus, it has been shown by me that there are three kinds of sperm, alike in form, but different in volume, all with the same amount of chromatin but with very different amounts of cytoplasmic substance; should it be shown that all three sizes of these sperm can fecundate the egg, then it might be possible that their different cytoplasmic amounts influence sex.

But those cases have proved of the greatest interest where the dimorphism of the sperm consists in their chromosome content. In 1891 Henking first described a modified chromosome that goes into only half the spermatozoa, and a pair of modified chromosomes were in 1898 discovered by me in spermatocytes of another insect. Since then chromosomes of both of these types have been made known in a large range of objects, especially insects, spiders, and myriapods, but also in certain vertebrates, including even man (Guyer). These modified chromosomes, known under a great variety of names, but most concisely as allosomes, seem to act differently from the other chromosomes only in paternal germ cells, and can be sharply distinguished from them. There is either a single one in male cells, in which case only half the spermatozoa come to receive it; or a pair of more or less unequal volume, in which event half the spermatozoa receive the larger and half the smaller. Then Wilson and Stevens, in 1905, found that in the maternal cells there is a pair in the place of a single one of the paternal cells, or a pair of equal ones in place of the unequal pair. To take one of the best known cases for illustration, the squash bug, oögonia contain 22 chromosomes, and all ripe eggs contain the reduced number, 11; but the spermatogonia contain 21 chromosomes, one less, and the spermatozoa either 10 or 11. McClung had in 1902 argued that the presence of the odd chromosome of the male cells determined the male sex. Wilson and Stevens, in 1905, showed this was not possible, for they demonstrated that males must come from eggs fertilized by sperm without an allosome, and females from eggs fertilized by a sperm with an allosome. This might be expressed as follows:

Sperm with allosome $\times$ egg with allosome = female, with 2 allosomes.

Sperm without allosome $\times$ egg with allosome = male, with 1 allosome.

Therefore Wilson and Stevens, and others after them, have argued that these allosomes or modified chromosomes may be true sex determinants, sex being a matter of their distribution in fertilization. Recently, for Echinoderms, Baltzer (1908) has shown just the reverse condition, that the egg cells are of two kinds with

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regard to their chromosome content, while all the sperm are of one kind.

This whole hypothesis has been recently critically reviewed by me (1910) so that there is no need of a further discussion of it here.

This hypothesis that sex is determined in fertilization by combination of certain modified chromosomes is not only not proved, but would seem rather improbable. The most we are justified in saying is that in some instances particular chromosome combinations coincide with a particular sex, which is very far from the conclusion that they are the causes of sex. It appears to me probable, and I hope to submit it to a test, that it is not a matter of chance into which daughter cell a particular chromosome goes, but that this is a regulated process; that two spermatids or two oötids are different in quality, and that one of them attracts the allosome while the other does not. This initial difference may be the one that determines sex, and the presence or absence of the allosome a secondary result of it. An observation that distinctly substantiates this view is that of Morgan, who found that in the reduction division of the male egg of Phylloxerans, two allosomes are regularly discharged from the egg into the polar body.

It is clear that any egg has two kinds of sex values that should not be confused, an actual and a prospective. Actually it is a female cell in distinction from the male sperm cell. This actual sex difference of the germ cells is established at or just after the last oögonal and spermatogonial divisions, for that is the time when it first becomes apparent; up to that time the two kinds of germ cells appear to be indistinguishable. The prospective sex value of the egg is with relation to the kind of multicellular body that it will produce, whether male or female. In a parthenogenetic egg there is no sperm to alter this first prospective sex value; it must be produced by the egg itself and probably before the maturation divisions, possibly during the conjugation of the chromosomes. Every egg must have such a first prospective sex value, whether it is to be fertilized or not. We do not know the causes engendering the sex potency, but it may well be determined by external factors, such perhaps as kinds of food, acting on the egg cells during their early growth period. Thus Russo claims that by injections of lecithin into rabbit does he has been able to modify the growth of their egg cells, and to secure a larger number of females among their offspring. Now, this first prospective sex value of an egg may be changed into another prospective sex value by the entrance of a sperm, certainly in some cases and possibly in all. Thus the sperm is sex-changing rather than sex-producing; it is a disturbing factor. And the sperm probably accomplishes this by modifying the metabolism of the egg, rather than by transmitting any particular sex determinants.

Sex is, accordingly, not an unchangeable character, but a state

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that may be shifted from one extreme to the other, as by the entrance of a sperm. Further instances of the changes of sex might be mentioned in the appearance of hermaphroditic individuals in species that normally have separate sexes; in the assumption of male characters by a hen into whose veins sperm of the cock have been injected; and in the development of masculine qualities by elderly spinsters.

At the basis of sex, as of every other quality of the organism, must lie metabolic physiological differences. An egg cell differs essentially from a sperm cell in producing a greater amount of substances; a female individual differs from a male in forming larger germ cells—and in many animals there appears to be no other differences between the sexes. Now, metabolism is chemical change started as a response to external stimuli. Therefore it should be possible to control the sex ratio by changing the conditions that affect the germ cells. But such experimental changes should operate very early, probably not later than the stage of the fertilized egg, and perhaps with best effect during the growth period of the germ cells. *January* 12, 1911.

MALARIA.

By William Pepper, M.D.,

(Abstract.)

This paper consisted merely of a résumé of the history of various discoveries which have been made in recent years in connection with this disease. Brief mention was made of Laveran's, Ross', and others' work, and the different varieties of malaria were described. The life cycle of the Plasmodium vivax was discussed in detail, serving as an example of the life cycles of the other varieties.

January 26, 1911.

OBSERVATIONS ON NATURAL AND EXPERIMENTAL YAWS.

By Henry J. Nichols, M.D.[1]

(Abstract.)

Yaws has shared in the remarkable progress made, during the last six years, in our knowledge of the etiology, diagnosis, and

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treatment of syphilis—its group relative. The organisms, while almost if not quite identical in form, set up different tissue reactions in man and in animals. The skin lesions of yaws are always the same and consist of raspberry-like growths covered with a yellow crust of dried serum.

Spirochetæ have been found in glands near a yaw, in 1 c.c. of circulating blood, and in the spleen pulp by puncture. The organisms, however, do not seem to be able to gain a permanent foothold except in the skin; there may be some fever and some pains in the joints but no definite lesions in internal organs or tissues have been found.

Auto-inoculation seems to me well established in man, and is in line with the incomplete immunity seen in many protozoal infections. A few scattered cases of positive Wassermann reactions have been recorded in the last few years, but in October last Baermann reported the results of over 100 examinations in Sumatra. Among fresh cases with a rich eruption he found 100 per cent. positive; in fresh cases with few yaws, 80 per cent. Among treated cases, 50 per cent. In some cases the reactions become negative after 2 or 3 injections of 1.5 grains of Hg salicylate, and in none except the fresh cases was the reaction strong.

In the Rabbit. A monkey was first infected on the eyebrow by rubbing in an abraded area an excised piece of a yaw. Some of the expressed serum from the monkey's yaw containing spirochetæ was then injected into rabbits' testicles. Three out of four rabbits became infected in an average of forty days. The strain has since been continuously kept up in rabbits, and is now in the tenth generation. About 65 rabbits have been used, and about 80 per cent. of inoculations have been successful. The serum reaction in rabbits develops in one or two weeks after the lesion and disappears as the lesion heals or is removed by castration.

In four animals I found that the spirochetes were immobilized and then disintegrated within twenty-four hours with a dose of 0.005 gram per kilogram of arsenobenzol. In 5 animals with similar lesions due to spirocheta pallida, the spirochetæ disappeared in forty-eight hours, but in 3 cases there was a distinct relapse after a few weeks with this dose. These results in regard to syphilis in the rabbit agree with those of Hata, and it seems probable that yaws can be cured with smaller doses of arsenobenzol than can syphilis. However, smaller doses than 0.005 per kilogram failed to destroy the parasites. *January* 26, 1911.

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PIROPLASMA (THE DEVELOPMENT OF PIROPLASMA PARVUM; THE CAUSE OF EAST COAST FEVER IN SOUTH AFRICA).

By K. F. Meyer, M.D.

(Abstract.)

Out of the group of the Binucleatæ one representative, the "piroplasma parvum," was selected for the description of the development of a protozoön belonging to the subgroup of piroplasma, causing a most fatal cattle disease in South Africa. The experimental study of this parasite was particularly carried out in the veterinary laboratories of the Transvaal. The development of this parasite has been studied and described by Gonder and K. F. Meyer. The development in the different organs and in the blood is about as follows: With the bite of an infected tick small nuclear forms of the parsaite are brought into the blood circulation. These are the *agametes* or *metagametes* which localize themselves in the hematopoietic organs, especially in the lymph glands, hemolymph glands, bone marrow, and spleen, where we find them in the developmental stages. If the lymph glands or the spleen are examined daily by means of punctures and the material is stained after the method of Schaudin, Giemsa, etc., the developmental forms can be easily recognized and distinguished from other pathological cells which may be present. After an interval of twelve or thirteen days, a period which varies with individual animals, we observe these agametes as small, roundish, intercellular, granular particles in lymphocytes, mononuclear leukocytes, and endothelial cells (especially bone marrow). They grow very rapidly and form a typical agamont. The intercellular forms are usually very rich in nuclei because a secondary infection with *agametes* will frequently take place. Under the influence of the parasite living in the protoplasma, the lymphocytes and leukocytes may succumb and the agamont becomes either free or breaks up by a typical schizogony into daughter cells. The successive division of the nuclei is affected amitotically. Very characteristic of this stage of the *agamogonous generation* is the structure of the numerous nuclei. They are irregular and of a clumpy, non-compact structure. They have not a very great affinity to stains, and are therefore very pale in stained preparations. At the time when the agamonts are formed the fever sets in. After a certain time the *gamogenous* or *sexual forms* begin to develop. An agamont, instead of forming agametes, shows reduction and formation of chromidia in its nuclei and forms typical gamonts which increase in size and number, and break up later by schizogony to *gametocytes*. These when in the red blood corpuscles represent the well known East Coast fever parasite. At this point the development in the intermediate host stops. In

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the *gamogenous forms* we have a strong, refractile nucleus having a great affinity to basic aniline dyes. Often in the youngest forms of the gamonts a small nucleus like the blepharoplast may be recognized. The multiplication of the nuclei in the gamonts takes place by primitive mitosis. From the gamont, when breaking up into the gametocytes, remains only a small roundish residual body of protoplasma. Generally the intercellular gamonts form more gametocytes than the free ones. This is due to double infection or to schizogony of agamonts within the lymphocytes; also the resistency of the lymphocytes is very important. The agamonts seem to have a more fatal effect on the lymphocytes than the gamonts. The effect on the endothelial cells is especially marked.

All the forms described have been observed for a long time by all investigators of East Coast fever, and Koch himself described these forms as bluish protoplasma disks or spheres of alveolar structure, containing in the plasma light or dark nuclei (Koch's granules or "blue bodies"). When looking over the literature we have to note one ingenious explanation for this developmental stage. Martin Mayer was of the opinion that the disease East Coast fever is not due to piroplasma, but to an invisible virus, and that Koch's granules are nothing else than products of a reaction on the lymphocytes or on the endothelial cells. Gonder and K. F. Meyer easily disproved this statement. The schizogony of the agamonts and gamonts can readily be observed in unstained preparations. The entering of the gametocytes in the red corpuscles is seen in every preparation made from the hemolymph gland. The gametocytes are present in abundance in the corpuscles at the end of the disease, and often we may observe four to five parasites in one red blood corpuscle. The parasite shows no development in the blood corpuscles and is harmless, producing never any toxins, and therefore no anemia occurs which is otherwise always observed in typical piroplasma diseases. If the animal does not succumb to the disease as it is observed in calves, the parasite gradually disappears from the blood and the fever drops naturally in the same way. No further development can take place in the blood of the cattle. All the following stages develop in the tick. Never parthenogenesis is observed. The recovery from one infection protects the body against relapses and an absolute immunity is present. No tick can infect itself on the recovered animal, and no infected tick can again produce the disease in this animal. The developmental forms in the tick are only recognized in certain uncorrelated stages, and further study has to be made.

CONCLUSIONS. The cattle disease, East Coast fever, is due to a protozoan which passes through characteristic developmental stages (agamogony and gamogony) in the lymphocytes, endothelial cells, and so on, and differs herein from the well-known piroplasma which have been reported up to the present time.

January 26, 1911.

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THE CHEMOTHERAPY OF EHRLICH, WITH SPECIAL REFERENCE TO THE TRYPANOSOME INFECTIONS.*

By B. T. Terry, M.D.

(From the Laboratories of the Rockefeller Institute for Medical Research.)

In his search for medicaments that might cure the trypanosome infections, Ehrlich[1] has reached two important conclusions. The first is that all chemicals which exert a curative effect on these infections are poisons. That is, they are capable, when given in sufficient quantity, of harming the vital organs of the host. In estimating the value of medicaments it is necessary, therefore, to compare the effect they have on the parasites with that they exert on the organs. The affinity the medicaments have for the parasites is termed *parasitropism;* that they have for the organs, *organotropism.*

For a medicament to have a practical value the proper relation should exist between the *organotropism* and the *parasitropism.* The *parasitropism* must be as strong as possible, and the *organotropism* as weak as possible. Under these conditions we may rid the body of the infecting parasites with the minimum of harm to the host.

Fixation. The second conception is simple, and to Ehrlich almost self-evident. It is that a parasite cannot be poisoned by a substance unless that substance can be attached or fixed to the parasite. For example, if arsenic is to injure the trypanosomes, there must be some means by which the arsenic may be attached. Should this mechanism not be present the trypanosomes could be suspended in the poisonous solution without being harmed. We shall soon see that there are solutions of arsenic in which the trypanosomes may be kept for some time without apparent harm, and others which destroy the parasites very quickly. According to Ehrlich, the difference in the action in these two cases is due to the fact that the trypanosomes have no mechanism for fixing the first solution, but have one for the second.

As a result of experiments that cannot be given here, Ehrlich believes that the fixation of various chemicals by the trypanosomes is brought about by the presence of definite chemoreceptors in the protoplasm of the parasites. These chemoreceptors have affinities for certain medicaments, and by means of these chemoreceptors the medicaments are attached to the trypanosomes.

This theory has been so productive in Ehrlich's hands that we will now apply it to results that may be obtained in the laboratory.

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There are, in general, two methods of testing the value of medicaments to be employed in the treatment of trypanosome infections. The first, or *in vitro* method, is to mix the medicament directly with the trypanosomes and observe the effect upon their morphology and motility. In these experiments one must remain within certain limits of concentration, for our conception of poison is relative, and innocent substances, such as sodium chloride, have a destructive and killing action on living tissues if the concentration is sufficiently great. In the second, or *in vivo* method, the curative value of the medicament is tested by injecting it into an infected animal and observing the result. In order to detect a slight action that the medicament may exercise it is necessary in these tests to inject the largest non-toxic doses.

The results of these two methods of testing medicaments may or may not agree. There are four possibilities, which we shall represent as follows: O O, + +, + O, and O +.

The first possibility, or O O, is that the medicament has no action either *in vitro* or *in vivo*. This is interpreted as meaning that the parasites have no chemoreceptors for the medicament employed, or else that the substance is not a poison.

The second possibility, or + +, is that both *in vitro* and *in vivo* the medicament has a positive action on the parasites. In this case we have evidence that the mechanism for binding the medicament is present in the parasites.

The third possiblitiy, or + O, is that the medicament *in vitro* may be active, but *in vivo* fail to influence the course of the infection. One of the most striking examples of this was found by Hata in Ehrlich's laboratory. In testing various substances upon different parasites, Hata was struck by the extremely toxic action methylene blue exerted upon the spirochetæ of relapsing fever, for this substance killed the spirochetæ even in a dilution of 1 to 6,000,000. In spite of this remarkable activity, the substance *in vivo* was a complete failure. Even when the dose employed was more than 500 times as large as would have been necessary to kill all of the organisms if the entire mouse had consisted of nothing but spirochetæ, the curative injection into an infected mouse did not have the slightest favorable effect. This means, according to Ehrlich's theory, that the spirochetæ have chemoreceptors for the methylene blue, but that the presence of these is rendered useless by the unfavorable relation which exists between the organotropism and the parasitropism. In this particular case the organotropism is more than 500 times as strong as the parasitropism.

The fourth and last possibility, or O +, is that the medicament *in vitro* exerts no apparent effect, but *in vivo* is found to have a curative action. This is the so-called indirect, or paradoxical action, and atoxyl is a well-known example. Atoxyl in weak or strong solution exerts *in vitro* a negligible action on trypanosomes, while

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in vivo, even in dilute solution, it is highly parasiticidal. In order to explain this we may assume that the trypanosomes have no chemoreceptors for atoxyl, but that the medicament, after injection into the animal body, is converted into another for which the parasites have chemoreceptors. The possibility of this conversion occurred to Ehrlich, for he knew from other work that the tissues of the body exert a reducing influence. In testing his theory Ehrlich reduced atoxyl in the chemical laboratory and obtained paraminophenylarsenoxyd. Solutions of this substance he then mixed *in vitro* with trypanosomes, and found that it immobilized the parasites in less than an hour, even when the substance was diluted one million times. Ehrlich believes that the substance produced in the animal body after the introduction of atoxyl is paraminophenylarsenoxyd.

The chemical explanation for the difference in action *in vitro* of atoxyl and paraminophenylarsenoxyd lies in the fact that in atoxyl the arsenic rest is pentavalent, and has, therefore, no additional affinities. In paraminophenylarsenoxyd, on the other hand, the arsenic molecule is unsaturated and has a valency of three. This latter substance, therefore, possesses additional affinities, by the aid of which it is in a position to combine chemically. In other words, the arsenic receptor of the trypanosomes is adapted, not to pentavalent but to trivalent arsenic.

There is another class of substances which show the paradoxical action. If a certain pyronin is mixed *in vitro* with trypanosomes in a dilution of 1 to 20,000 or 1 to 60,000, it has, according to Ehrlich, no apparent action on the parasites. Nevertheless, if the mixture of the medicament and actively motile parasites is injected into a susceptible animal no infection takes place. In this case Ehrlich offers an entirely different explanation. In spite of the apparent lack of action, he assumes that the parasites have chemoreceptors for pyronin, and that the medicament is therefore bound to the parasites. The lack of effect *in vitro* is explained as being due to the fact that the medicament is fixed to some part of the parasite which does not influence motility or morphology. This part Ehrlich considers to be the one governing reproduction. The injected parasites have, therefore, been injured in spite of their normal appearance, and the injury consists in a sterilization. No infection followed the introduction of the parasites, for the reason that the trypanosomes were no longer able to reproduce their kind, and quickly died out after being injected.

In support of the view just given Ehrlich cites the results of Busk, who found that certain ciliates, paramecium for example, could live for weeks in a strong solution of trypanred. Busk observed, however, that the parasites did not increase in number, and found that the sterilizing action of trypanred was exerted even in very dilute solutions.

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According to Ehrlich, this conception may have a very practical application. If the therapeutic dose of a *sterilizing* medicament is very much less than that of another which destroys all of the organisms, it will be possible to use very much smaller quantities of the former and yet obtain the effect of the latter, for in an infected animal the sterilization of all of the parasites is equivalent to killing all the organisms, when the life of the individual parasites is measured by a few hours or days. The smallness of the dose is important, for the reason that all medicaments that are parasiticidal are, according to Ehrlich, poisons, and the less we have to give, the greater the chance of treating without doing harm to the host.

We have thus far considered normal trypanosomes. Let us now apply Ehrlich's chemoreceptor theory to abnormal or resistant trypanosomes, for in Ehrlich's laboratory it was found that trypanosomes could be rendered resistant to treatment, and strains of this kind have now been produced against representatives of each group of medicaments known to be active against trypanosomes.

Resistant strains differ from the normal in that it takes more medicament *in vitro* to kill them, and when the resistance is high, it becomes impossible to destroy the parasites in the animal body by injecting the medicament against which the resistance has been acquired. According to Ehrlich's theory, the chemoreceptors of the trypanosomes that acquire a resistance to medication have suffered a loss of avidity for the medicament that they normally bind.

This loss of avidity of the chemoreceptors is a purely chemical conception. In the parasites there is no morphological change corresponding to it. Moreover, the loss is relative, not absolute. The diminution in the avidity is merely to the extent that the resistant trypanosomes are unable to take up the medicament in the concentration in which it is present in the body fluids of the species of animal in which the resistance was developed.

Curing Resistant Strains. As Ehrlich had shown that resistant strains could be made in the laboratory, it was important to find some means of curing these strains, as it was quite possible that resistance might be produced unintentionally in the treatment of trypanosome infections. He therefore set himself the problem of curing animals infected with trypanosomes rendered resistant to atoxyl, and after a number of months found a medicament that could do this. This was arsenophenylglycin.

Ehrlich then attempted to produce a resistance to arsenophenylglycin, and again, after a certain number of months, succeeded in securing trypanosomes that could no longer be cured by this medicament.

In attempting to explain the resistance of trypanosomes to arsenophenylglycin, Ehrlich first assumed that the affinity of the arsenic receptor of the trypanosomes had undergone a further

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reduction. This conception, however, he soon discovered was incorrect, for, on testing, *in vitro*, the trypanosomes resistant to atoxyl and those resistant to arsenophenylglycin he found that it took just as much paraminophenylarsenoxyd to kill one as it did to kill the other. From this it was evident that the chemoreceptors for arsenic had not been altered.

Another explanation was, therefore, necessary, and this was soon forthcoming, for Ehrlich found a number of medicaments (derivatives of phenylarsenic acid) which, like arsenophenyglycin, could cure animals infected with the atoxyl resistant strain. He noted, moreover, that all of these medicaments were alike in one respect—they all contained the radical of acetic acid, CH_3COOH. He drew the conclusion, therefore, that arsenophenyglycin had acted by means of its acetyl group, and that when the strain resistant to arsenophenylglycin was produced the acetyl receptor had suffered a diminution in its avidity for the corresponding group in the medicament.

From this it would appear that trypanosomes have at least two chemoreceptors by which arsenophylglycin may be fixed—the *acetyl* and the *arsenic* receptors. According to Ehrlich, both are active in binding the medicament. Believing that the acetyl receptor is the first to come into play, he calls this the *primary haptophore*, and the arsenic receptor the *secondary haptophore*. This process by which a medicament is bound, first by one receptor, and then by another, Ehrlich has likened to the pinning out of a butterfly, in which the first pin fixes the body, the next one wing, the next the other wing, and so on.

Aiming. Ehrlich regards it as highly important to learn the chemoreceptors possessed by the parasites, because this knowledge can then be used to enable one to *aim* directly at the organisms we wish to destroy. For if we know all the chemoreceptors a parasite has, we can then attach corresponding side chains to some of our active radicals, *e. g.*, Hg, As, or I. In this way we may force the poisonous substances on the parasites, and with deadly effect. An example will help to make this clear.

In testing various medicaments Ehrlich employed in one instance a substance that had an action on both trypanosomes and spirochetæ. He wished to increase the activity of this medicament for the spirochetæ. As iodine has a decided curative effect on syphillis, he concluded that certain spirochetæ must have iodine receptors. He therefore introduced iodine into the medicament and then tested it once more. The result showed that its destructive action for the spirochetæ had increased greatly.

The problem is, however, not at all a simple one. Although the introduction of iodine increased the value of the medicament for spirochetæ, it did not leave unchanged its effectiveness against the trypanosomes, since on testing it on these organisms its activity was

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found to have greatly decreased. This is to be explained, according to Ehrlich, by assuming that the introduction of iodine so altered the relation of the arsenic group that the chemoreceptor for this group could not act as freely as usual. In support of this conception Ehrlich cites an example in which two chemicals unite ordinarily only at a high temperature. The introduction of a side chain into one of these chemicals so altered its relation to the other that they could combine at room temperature. The introduction of a second side chain, however, made the reaction as difficult as in the beginning, and the addition of another side chain made the union still more difficult.

Steps in Chemotherapy. We may now give briefly the steps by which medicaments are found and improved. First of all, it is necessary to secure substances which have some action on the parasites we are trying to destroy. The attempt is then made to determine the active groups in the medicament, and when these are known, or even before, one begins to make chemical variations in the substance with the hope of increasing its parasitropism and decreasing its organotropism. This means that we must select from our stock of chemical variations the ones which are best for therapeutic use.

Best Medicaments. In the selection of the best medicaments several points must be borne in mind:

1. The medicament should be *safe.* The curative dose must bear the proper relation to the lethal dose. If the former is eight or nine-tenths of the latter, the medicament is too dangerous to use, unless the case is desperate and nothing better is at hand. Moreover, the medicament should not easily give rise either to resistant strains among the parasites or to hypersensitiveness in the patients.

2. The medicament should be *efficient.* It should cure the largest possible number of species of trypanosomes, and also the largest possible number of hosts infected with these strains. It is highly desirable, furthermore, that it should be able to cure the resistant strains that are apt to have been produced by previous treatment.

3. The medicament should be one that it is *convenient to use.* It should be easily administered, give rise to little pain, and be followed by no disagreeable or serious consequences, such as ulcers, necrosis of the skin, loss of hearing, or blindness.

4. The action should be *rapid* and *sure.* When the best medicament for the treatment of laboratory animals has been found, it becomes necessary to introduce it into practice. In the case of human therapy this is very difficult, for it is not possible quickly and easily to ascertain how much of the drug a man can stand. We must begin with very small doses and gradually increase these as we find it is safe to do so. In this way we can eventually determine the maximum tolerated dose.

As a model of the way a medicament should be introduced into

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practice, we may take the 606 of Ehrlich and Hata. At first this medicament was intrusted only to hospitals and skilled workers, and was given free to these with the request that, in the beginning, only cases of a certain kind be treated, that careful records of the results be kept, and that these should be communicated promptly to Ehrlich. In this way the instructions which accompanied each supply of medicament that left the laboratory could be based upon the latest experimental results, and the dose could be raised as rapidly as was safe. Some twenty to thirty thousand patients were thus treated before the medicament was placed upon the market.

We may now summarize the points of most importance in introducing a medicament into human therapy. (1) *Uncomplicated* cases should be selected in order that the action upon the disease studied may be ascertained without being obscured by the effect the drug may exercise upon some one or more of the complications. (2) *The cases chosen should not previously have been treated,* for experience has shown that the administration of one medicament may render the host hypersensitive to the influence of another. For example, it has been found that atoxyl treatment renders the host hypersensitive to acetyl-atoxyl. When sleeping sickness patients received acetyl-atoxyl after they had been treated with atoxyl, alarming symptoms appeared—symptoms that were not seen at all, or but rarely, in the treatment of patients that had not previously received atoxyl. (3) The cases selected for treatment should be *early* ones, since experience teaches us that the later stages are much more difficult to treat. If a medicament should be judged merely by its effect upon the later stages, many useful remedies would be discarded, and the opportunity of using these as a base from which to work for more effective substances would be lost.

Best Conditions. After selecting the right patients, these should be put under the best possible conditions for observation and treatment. (1) They should be put to bed, if possible, several days before the beginning of treatment, in order that the effect of rest upon the disease may not be attributed to the medicament. (2) The diet and bowels should be regulated, and the pulse, temperature, and respiration kept under observation. (3) Prolonged, careful records of the cases should be kept, in order that data may be at hand for determining the following points: The indications and contraindications for treatment, the dose, and the proper method of administering the drug.

The Treatment. In general, there are two methods used in the treatment of trypanosome infections—the intermittent and the energetic. In the intermittent form a dose which is insufficient to cure the animal is administered repeatedly with intervals of a number of days between. The hope is entertained that the repetition of the small doses at these rather considerable intervals may even-

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tually cure the animal. In the treatment of rabbits this method has given good results, but with other animals the effect has been less favorable, and in many cases bad.

By the second, or energetic method, only one treatment is given. This may consist of a single injection of the medicament, or of two large injections within forty-eight hours. When these are given the treatment is stopped, and is not again repeated if bad symptoms do not return.

Avoid the Intermittent. In the treatment of sleeping sickness with arsenophenylglycin Ehrlich thinks that the intermittent form of treatment should be abandoned. He gives three reasons.[2]

1. It is *ineffectual.* A given small dose of medicament which fails to rid the body of the parasites when first introduced is no more able to do this when repeated a number of days later.

2. The intermittent method may lead to *hypersensitiveness* on the part of the patient, and this is doubly dangerous, since the symptoms that follow hypersensitiveness make it impracticable to increase the quantity of the medicament given, and the original dose becomes less and less effective as the tissues of the hypersensitive host bind more and more of the drug.

3. This is the method by which *resistant strains* are produced, and resistant strains constitute one of the most serious dangers in the treatment of trypanosome infections, for they make the cure of the patient exceedingly difficult, if not impossible.

Three Groups of Medicaments. As the result of testing perhaps thousands of preparations we have at the present time three groups of medicaments that are active against trypanosome infections. These are as follows:

1. The arsenic and antimony group. The most important arsenic preparations are arsenious acid, atoxyl, acetyl-atoxyl, arsenophenylglycin, and, last of all, 606. Of the antimony compounds we may mention the antimonyl tartrates of potassium and sodium, aniline antimonyl tartrate, and the antimonythioglycollic acid compounds.

2. The group of azo dyes. Examples are trypanred, trypanblue, and trypanviolet.

3. The group of basic triphenylmethane dyes. Here we may mention parafuchsin, pyronin, and tryparosan.

Of the medicaments thus far tested, the one which has given the best results in the largest number of trypanosome infections in the largest number of hosts is arsenophenylglycin. In the treatment of mice, rats, and rabbits a single dose suffices to cure. The medicament has also been of considerable value in the treatment of larger animals and of man. But its use has shown that the trypanosomes in various parts of the world react in a most variable manner. According to the way the parasites respond to treatment, Ehrlich divides them into three classes.

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1. The favorable case, or *casus faustus*. Here a single dose suffices to cure, and the dose employed is only one-half or one-third of the highest tolerated dose. In the laboratory many examples of this have been met with. Ehrlich cites here the results of Strong, who, with a single injection that was only about one-half of the lethal dose, cured 90 per cent. of the monkeys (*Cynomolgus philippinensis*) infected with surra.

2. The doubtful case, or *casus dubius*. The medicament may cure, but the necessary dose is close to the toxic one. Medicaments which give this result may still be used to advantage in the treatment of animals that are sure to die unless treated. As an example, Ehrlich refers to the results of Strong, who found that arsenophenylglycin could save one-third to one-fifth of the horses naturally infected in the Philippines. Strong recommends, therefore, the use of arsenophenylglycin in the treatment of all valuable horses infected with surra.

3. The unfavorable case, or *casus infaustus*. The resistance to treatment is so great that the medicament fails altogether to cure.

The first thing to find out in practical therapy is in which of the three categories the case to be treated falls, and then to adopt the proper measures. In case two, for example, combination treatment should be resorted to. Broden is now using tryparosan in combination with arsenophenylglycin with excellent results, where arsenophenylglycin alone had proved unsatisfactory.

In Uganda, also, arsenophenylglycin has proved far from satisfactory in the treatment of sleeping sickness. The fact that many of the cases treated were very advanced may partially explain the result, but it seems practically certain that the parasites there have an unusual resistance to arsenic.

As a contrast to the result in Uganda, the experience of von Raven in Togoland should be referred to, for the sleeping sickness organisms there seem to be as easy to treat as in Uganda they are difficult. "Of twenty-three patients . . . who received, two days running, from 0.7 gram to 1.2 grams arsenophenylglycin, all were well twelve months later."[3]

District Treatment. As a consequence of the remarkable variations toward the curative action of a given drug shown by trypanosomes in different regions, Ehrlich suggests that it may be necessary to adopt a form of *district treatment.* This may mean that parasites will be obtained from the regions where the usual forms of treatment are unsuccessful, taken to the laboratory, and there studied with the purpose of securing a form of treatment that shall be adapted to the infections in these particular regions.

Whether this be necessary or not will probably depend upon the results obtained with newer medicaments, for it is always possible that some may be found which will have a wider applicability than any yet tested.

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606. The only other medicament that we shall mention is 606. This has proved to be of value, not only in the treatment of spirochetal infections, but also in those caused by the trypanosomes. After satisfactory results had been obtained in animal experiments, Ehrlich sent some of the medicament to Broden in Africa, and the latter found that an injection of 0.3 to 0.6 gram of 606 caused the parasites to disappear promptly from his patients. The time, however, is too short for us to be able to form a judgment concerning the permanency of the result.

While it is quite possible that the best medicaments for the treatment of the trypanosomiases have not yet been found, the situation is not at all discouraging, for the way to secure active curative agents is now known with exactness. If the medicaments in our possession prove inadequate, we have but to continue our search until the right ones are found.

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January 26, 1911.

SPECIMENS PRESENTED FEBRUARY 9, 1911.

Dr. D. B. Pfeiffer for Dr. A. O. J. Kelly:

Hydatiform Mole.

The specimen consists of a uterus with both tubes and ovaries which had been removed at operation by Dr. John B. Deaver.

The patient was a Russian Jewess, aged fifty-two years, she had had nine labors and three miscarriages, the last eight years before operation.

The menses had been regular but very scanty for the last two years; for three months she had been bleeding constantly and had suffered from pelvic pain, loss of appetite, and nausea after meals.

The uterus was symmetrically enlarged and about ten times its normal volume, and when opened disclosed a typical hydatiform mole which was everywhere closely applied to a thickened and succulent decidua.

No trace of a fetus was found, there was no evidence of malignancy grossly or microscopically. The tubes and ovaries were normal and in the left ovary was found the corpus luteum of pregnancy which presented no unusual features.

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DR. ALLEN J. SMITH:

Ova of Schistosomum Japonicum; Ova of Schistosomum Mansoni; Ova of Paragonimus Westermanni.

The ova of Schistosomum japonicum were obtained from a young white boy, the son of an American missionary in China, probably the first recorded case of this type of schistosomiasis in a Caucasian. Evidence points to the acquirement of the disease by penetration of an early stage of the parasites through the skin while the boy was wading, in consonance with Katsurada's findings in experimental infestment of animals. The specimens shown are in the early, unexpanded state. At about 30° C. in the course of ten to twenty hours these eggs expand to nearly or quite double their capacity and the miracidium, now seen in quiescent stage, moves actively about within the enclosure; and with further enlargement, the wall of the ovum splits and the embryo escapes as a free, swimming, ciliated organism. In our laboratory we have placed water containing large numbers of such free miracidia upon the skin of puppies for varying periods and then removed the skin for microscopic examination, but have failed to find them in the tissues. Animals thus exposed, and one with several cubic centimeters of water containing probably fifty or a hundred of the living miracidia injected under the skin, have failed thus far (six weeks) to show evidences of having been infested. Further work is now in progress to determine whether the infesting stage of the fluke, which surely gains access through the skin, is the miracidium or perhaps the cercaria, developed in some intermediate host as a leech or snail.

The eggs of the Schistosomum Mansoni exhibited were obtained from Porto Rico, from the stool of a patient in charge of one of the Naval surgeons stationed there. It shows well the lateral spine as the principal diagnostic feature of the specimen.

The ova of Paragonimus Westermanni were obtained from the contents of a bronchiectatic cyst (of which there were four in the lungs), containing the adult specimens of the lung fluke, in the lungs of a wild cat from South Carolina, the animal having recently died in the Philadelphia Zoölogical Gardens. I present it by favor of Dr. Fox, the pathologist of the Gardens; and wish to point out the fact that this discovery extends very materially the distribution of the lung fluke in this country. It has been found on the Pacific coast in man, in the cat in Michigan, in the hog in Cincinnati, and here in the south and east of the Alleghanies. It is practically sure, when one considers such distribution, that the parasite will eventually be found in man as a definite parasite of this country; and I would urge careful examination of the unstained sputum of all cases showing slight persistent hemoptysis for the eggs of the parasite.

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DR. EDWARD H. GOODMAN:

The Isolation of Copper from the Urine and Sweat of a Brass Worker.

(From the Laboratory of Dr. John H. Musser.)

As far as I have been able to gather from the literature, the reports of so-called brass poisoning have to do only with the clinical aspect, and since to my knowledge there has been no reference made to the output of copper in these cases, one must suppose that no attention has been devoted to this side of the question.

The case which I report this evening has been studied from this point of view, and since it presented some unusual features, I judge it worthy of discussion.

The patient, aged fifty-nine years, brass worker by trade, was admitted to my dispensary in the University Hospital, October 21, 1910, complaining of pain in epigastrium with loss of weight and of strength. The general history was without interest except that which pertained to his occupation. He has been working in a brass factory for forty-seven years, and has worked in all departments of the same. He describes having at various times a "brassy" taste in his mouth, and has also noticed green sweat. He was questioned more closely as to the latter and asked if the so-called sweat could not have been due to mechanical deposition of brass. This was not the case, however, since he said that in summer after a day's work, he would go home and bathe thoroughly and that the following morning his bed-linen would be stained green.

The case was to me of such unusual interest that I asked him to bring a twenty-four hour portion of his urine and his undershirt, which he said was undoubtedly stained green. This he did, and the latter (demonstration) showed unmistakable greenish areas. That this was not due to rubbing against copper articles, etc., was emphatically stated by the patient, who said he always wore another shirt outside this one.

The urine (1090 c.c.) was evaporated on a water bath, the residue charred and taken up in hydrochloric acid with moderate warming. The acid solution was heated in a beaker to 80° and H_2S conducted into it slowly with the temperature of the beaker contents kept at 80° C. This was continued for a half hour, the precipitate allowed to settle and filtered. The precipitate was washed with hot water, first with the addition of HCl, and dried on the filter.

The filter and precipitate were burned in a Rose crucible and the cupric sulphide covered with fine powdered sulphur and hydrogen conducted through the hole in the lid by means of a porcelain pipe. This was continued for five to ten minutes and the crucible slowly heated.

Weight of crucible and residue	15.7830
Weight of crucible	15.6850
Weight of copper sulphide	0.0980

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Since 100 parts Cu_2S equal 79.85 parts copper, so we have 0.0782 gram copper.

After weighing, the residue was dissolved in the warmth with strong nitric acid, then diluted, and qualitative tests made with potassium ferrocyanide, sodium sulphide, glucose and ammonia. All were positive except the last, and I believe there can be no doubt as to the existence of copper.

Without estimating the quantity of copper in the shirt, which has but little importance, qualitative tests were made. In order to preserve the shirt as intact as possible, a piece was cut out, dissolved in nitric acid and the customary tests made. Copper was found.

Books on toxicology mention no such case, and a review of the shorter papers on brass poisoning was also without success. In how far brass itself is the cause of the intoxication, it is impossible to say, the general view being that the copper ingredient must be held as the poisonous agent.

A SCIENTIFIC STUDY OF THE DETERIORATION OF POULTRY DURING MARKETING.

By M. E. Pennington, Ph.D.

(From the Food Research Laboratory, Bureau of Chemistry, United States Department of Agriculture.)

The facts which I am to present to you tonight are illustrative of a broad, far-reaching endeavor on the part of the United States Department of Agriculture to prevent the enormous waste which now occurs because of the deterioration of perishable products between the producer and the consumer, a deterioration due almost entirely to bad handling. That you may grasp the scope of the field of endeavor let me quote a paragraph from the close of the annual report of the Secretary of Agriculture for the year 1909:

"It will be observed that more and more attention is being directed to the study of the handling of perishable products, that waste may be lowered and quality and condition improved. Such investigations as have been conducted in California on the handling of citrus fruits and table grapes; in Georgia on the handling of peaches; the handling of poultry and eggs, oysters, corn, wheat, flaxseed, milk, codfish, sweet ciders, etc., indicate the breadth of the work now in progress. The results already obtained show the great value and importance of such studies in the conservation of our finished products—the most valuable asset of any people."

In this list of perishable products which the Department of

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Agriculture is now studying, foodstuffs predominate, and properly so, since undoubtedly the days of an abundant food supply for us have passed, never to return; hence it behooves us not only to save from actual destruction, but to bring to the consumer in the best possible condition all the foods which we produce.

What must be the aggregate loss, represented in dollars, due to deterioration of all of our perishables throughout the country can be imagined when we consider the few specific instances where investigation has gone sufficiently far to permit of making estimates. The citrus fruit growers of Southern California, utilizing some pioneer investigations of the department in the handling of oranges and lemons, have practically eliminated decay, thereby saving about $1,500,000 worth of fruit each year in Southern California. The great apple industry of our far northwest is based on the careful handling of the fruit that it may carry safely to the Atlantic seaboard and hold its beauty even after months in the cold stores. This industry could not exist without the scientific research work of plant pathologists, and chemists, and pomologists, and its value amounts to many millions annually.

With such achievements won, the Department a short time ago undertook to investigate the handling of poultry and eggs—a crop standing high in economic importance. The estimated value of the eggs produced in this country in 1909 is over 500,000,000 dollars; the value of our poultry is not far from that sum. A study of the poultry and eggs offered for sale on the market indicates that at least 10 per cent. of the output is either lost as a food, or of lowered quality due to deterioration on account of bad handling.

To the Food Research Laboratory of the Bureau of Chemistry has been assigned the investigation of the handling of poultry and eggs, to the end that the supply may reach the consumer in good condition and that the millions of dollars which are now lost annually may be saved. The work has developed from strictly laboratory beginnings on one relatively small phase of the subject, namely, cold storage, until step by step every branch of the industry —pedler, packer, transportation agencies, warehousemen, commission men, retailers, and even the consumers—most ignorant of all—has been invaded and has become interested, each now cooperating with us to advance the object of the research. The cooperative work with the industry, however, is another story. The chapter to which I would call your attention now is the application to chicken flesh of a few laboratory procedures in chemistry and bacteriology which yield results which indicate more accurately and closely than sight, smell, or touch, the amount of deterioration which the flesh has undergone.

As an illustration of the problems in decomposition to which these methods are applicable I have chosen a study of the relative rate of deterioration in fowls eviscerated in several ways as compared with those having the viscera *in situ*.

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There has been much discussion on the part of the public concerning the wholesomeness of undrawn poultry. In many States the matter has been presented to the legislators in an endeavor to exclude all uneviscerated poultry from the market. In some places such laws have been passed. Conflicting testimony has resulted concerning the relative keeping time of drawn and undrawn birds. Since the question is one which affects both the health of the people and the welfare of the industry, exact information on the subject is desirable.

Experience has shown that such problems as this cannot be solved by preparing specimens in the laboratory and reproducing the trade cycle as nearly as possible in laboratory surroundings. If results are to be applied to the industry, the experiments must be carried on under strictly commercial conditions and in commercial quantities.

This principle has been used in the study of the question under discussion. The birds were killed and dressed in a Kansas packing house, shipped to an eastern market centre in refrigerated cars, and handled at the market by a commission man and a retailer. All the work was very well done, commercially speaking, and the specimens were strictly comparable except for the presence or absence of the viscera.

"Drawing" as understood in the poultry industry may consist in a more or less complete removal of the viscera. The trade terms are "undrawn," "wire drawn," Boston drawn," and "full drawn." The differences are explained by the following outlines of the methods of preparation;

1. *Undrawn Fowls.* Shipped with viscera *in situ,* heads and feet on, and no incisions except for bleeding and braining.

2. *Wire Drawn.* This consists in pulling out a loop of intestine by inserting the finger through the vent, cutting the loop, and drawing out the gut by careful traction until it breaks at the gizzard. The vent of a bird so drawn presents a normal appearance; the only indication of drawing is the collapsed abdomen.

3. *Boston Drawn.* This is a modification of wire drawing, in that a circular incision is made around the vent and the intestines pulled through until rupture occurs at the gizzard.

4. *Full Drawn.* The body cavity was opened by a transverse cut across the abdomen, and the vent was removed by cutting around it. The head was cut off and the intestines and viscera completely removed. The heart, liver, and cleaned gizzard, as well as the excess body fat, were put back into the body cavity. The shanks and feet were removed and the hocks were thrust through the opening in the abdomen and the vent.

The full drawn birds are subjected to the greatest amount of bacterial contamination, the Boston drawn and wire drawn standing next in order of cleanliness, and the undrawn are exposed the least.

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As compared with such contamination, arising from the leakage of ruptured intestines, dirty surroundings, etc., is the migration of organisms from the intestine of the undrawn birds into the flesh. Since the decomposition of flesh hangs upon bacterial invasion and proliferation, the relative number of organisms present is of importance. Accordingly, twenty-four hours after the killing and dressing of these birds, by which time—having been kept in a room artificially refrigerated to a temperature of 32° to 38° F.—the animal heat was removed, a count was made of the organisms in one gram of the flesh of the body wall, including the lining membrane and the muscle beneath it. The average results of 11 experiments are given in Table I, which shows but a low number of bacteria in the flesh of the undrawn, as compared with the drawn fowls. After the fowls had reached the commission man at the market centre, which in these experiments necessitated a seven days haul, another examination gave bacterial counts as indicated under Sample 2, Table I, showing a still wider difference between the birds which had been subjected to contamination by handling and those which were untouched.

TABLE I.—*Increase in number of bacteria per gram in the flesh of the body wall during marketing, comparing four methods of dressing fowls.*

(Plates incubated at 20° C.; average for 11 shipments.)

Style of dressing.	Packing-house sample. (1)	Commision house sample. (2)	First sample from retailer. (3)	Second sample from retailer. (4)
Undrawn . . .	236	10,790	168,170	1,468,000
Wire drawn . .	68,864	82,648	5,481,640	50,759,300
Boston drawn . .	23,234	341,650	34,258,000	20,309,000
Full drawn . . .	77,580	9,523,000	1,885,710,000	5,375,270,000

The two samples taken during the sojourn of the chickens in the shop of the retailer accentuated the difference. At the close of the experiments the number of bacteria per gram of the flesh of the body wall was in all cases high enough to show staleness; the full-drawn specimens were frequently not edible. The decisiveness of the bacterial count, alone, is sufficiently conducive evidence of the relative state of preservation of the flesh. However, as additional information, organisms of the coli group were sought with the result that they were found in the walls of the abdominal cavity in 30 per cent. of the undrawn fowls when they reached the retailer, and in 90 per cent. of the full drawn. Twenty-four hours after killing the well-handled undrawn fowls did not show intestinal organisms in the flesh of the body wall, but 80 per cent. of the drawn specimens were so infected. Hence it would seem that the chief source of contamination was the dressing itself.

The method followed for the quantitative bacteriological analysis

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of the flesh has been given in Bulletin 115, Bureau of Chemistry, United States Department of Agriculture.

A complete chemical analysis of flesh, to determine deterioration from the food viewpoint, is so complicated and time-consuming that a large force of analysts would be required to handle any number of samples. It has been the aim of our work, therefore, to determine accurately and rapidly certain chemical changes which have been proved by experience to indicate alterations in its composition. For example: The amount of free acid in the fat of the chicken has been found to be an excellent indicator of its freshness. The usual method for the estimation of free fatty acids, which is cumbersome, has been so modified that the result can be obtained in a few minutes. The details of these modifications, as well as a general statement concerning their significance in the detection of aging flesh, has already been reported (*Journal of the American Chemical Society,* Pennington and Hepburn, vol. xxxii, No. 4, p. 568).

TABLE II.—*Changes, during marketing, in the acidity of the fat, comparing different methods of dressing.*

(Percentage of free acid; average for 11 shipments.)

Style of dressing.	Packing-house sample. (1)	Commission-house sample. (2)	First sample from retailer. (3)	Second sample from retailer. (4)	Percentage of increase.
Undrawn	0.47	1.25	2.27	2.90	517.02
Wire drawn . . .	0.44	1.12	2.10	3.20	627.27
Boston drawn . .	0.39	1.33	2.51	4.09	948.72
Full drawn . . .	0.53	1.38	4.22	7.82	1375.47

As applied to the work under discussion it has given the results shown in Table II. The fat of a chicken immediately after killing is neutral; at the end of twenty-four hours with proper chilling the acid value (that is, the number of milligrams of caustic potash required to neutralize one gram of fat) is still less than 1, generally about 0.8; estimated as free oleic acid, it is approximately 0.4 per cent. It will be seen that the acidity of the fat of the chickens dressed in various ways was about the same when the packing house examinations were made, though the average shows a very slight rise in the full drawn samples. But from the time the birds reached the market until the end of the experiment there were wide differences between them according to the manner of dressing, the undrawn showing the lowest and the full drawn the highest acidity. It is of interest, also, to note the percentage of increase for each form of dressing, from the packing house sample, when the birds were perfectly fresh, to the last retail sample, when they were either distinctly stale or really inedible.

One of the most valuable indications of flesh decomposition which we possess is the quantity of protein nitrogen which can be

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split off by weak alkalies in the form of ammonia. The methods which have been in use for the estimation of the ammoniacal nitrogen in meat, unless it was present in large quantity, were unsatisfactory. However, it is the small increase which is most important from the food viewpoint. An adaptation of the Folin method, using a very strong current of air and a longer time than is required for the expulsion of ammonia from a liquid, gave definite results on very minute quantities of ammoniacal nitrogen.

Fresh chicken flesh contains about 0.012 per cent. of nitrogen in this form. As the flesh ages, the amount increases, though the percentage of increase is not so pronounced as in the case of the fat acidity. Yet even so, the difference between the increase for the undrawn specimens, which is about 19 per cent., is very striking when compared with the increase of 53 per cent. shown by the full drawn. These figures, as well as the percentages of ammoniacal nitrogen in the samples at the various periods of marketing are given in Table III.

TABLE III.—*Percentage of ammoniacal nitrogen present in the flesh during marketing, comparing different methods of dressing.*

(Average for 11 shipments.)

Style of dressing.	Commission house sample. (2)	First sample from retailer. (3)	Second sample from retailer. (4)	Percentage of increase.
Undrawn . . .	0.0129	0.0139	0.0153	18.60
Wire drawn . .	0.0128	0.0145	0.0154	20.31
Boston drawn . .	0.0125	0.0134	0.0158	26.40
Full drawn . . .	0.0120	0.0151	0.0184	53.33

From the viewpoint of the acquirement of facts concerning flesh decomposition, these simultaneous determinations of the number of bacteria, the amount of loosely combined nitrogen, which has commonly been referred to bacterial activity, and the free acid in the fat, a change due very largely to enzymic action, is of more than passing interest. Taken in connection with the fact that, so far as possible, every detail of environment has been noted from the time the chicken was picked up to be killed in the State of Kansas until it was due to be sold to the consumer in New York, the study acquires a much broader significance, since effect can be traced to cause, and the scientific finding can be applied to the betterment of market stocks.

Studying flesh decomposition on this plan, that is, a detailed record of environment and handling, and every resource that the laboratory can afford to put the results of such conditions on a definite basis which is independent of the personal equation and the varying standards of visual inspection, must make for an advance in the quality of the food supplied to the people.

February 9, 1911.

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A PRELIMINARY NOTE UPON THE ENZYMES AND THE LEUKOCYTES IN ACUTE LEUKEMIA.

By Warfield T. Longcope, M.D., and J. V. Cooke, M.D.

(Abstract.)

A few years ago one of us (Longcope) with Dr. Donhauser had an opportunity to study a case of acute leukemia in which 80 to 95 per cent. of the cells at different times were of the large uninuclear type, rich in protoplasm which, however, rarely contained neutrophilic granules when stained in Ehrlich's triple stain.

Stimulated by the work of Opie we made some studies of the enzyme action of these cells and found that they contained a ferment which digested protein actively in neutral and alkaline solutions. Control experiments showed that the leukocytes from the blood of a case of chronic myelogenic leukemia acted in the same manner. Polymorphonuclear leukocytes from pus produced by non-proteolytic bacteria acted in the same manner as the cells from the blood of the case of acute leukemia. It was therefore evident that these cells from the acute leukemia contained what Opie has termed leukoprotease, a trypsin-like enzyme. Though no autopsy was obtained an enlarged lymph node was removed and found to contain leukoprotease. Sections of the gland showed that the normal structures were in large part replaced by the large cells like those in the blood and tests showed that the gland was rich in leukoprotease.

Experiments with lymph nodes removed at autopsy from a case, a chronic small cell lymphatic leukemia which could not be studied during life, gave no leukoprotease. Lymph nodes from cases of typhoid fever rich in the large phagocytic cells yielded an enzyme which acted exclusively in acid medium and therefore corresponded to pepsin.

We concluded that the presence of leukoprotease in these large cells was strong evidence that they were closely related to the granular series of white cells of the blood, and should be considered, as had already been done by a number of observers on morphological evidence as non-granular myelocytes.

Since then we have had no further opportunity to extend these observations until quite recently. During this time, however, other observers, notably Marie and Fiessinger have noted proteolytic enzymes in the cells from so-called large cell lymphocytic leukemia and recently Graetz has used these biological principles for a differentiation of cases of acute leukemia.

Within the last few weeks it has been possible to study a second case of acute leukemia. Unfortunately blood could not be obtained

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for experiments during life, but immediately after death a trocar was put into the heart and large quantities of blood drawn into citrate solution. The clinical course of the disease which occurred in an Italian, aged thirty-three years, was rapid, lasting about five weeks, and was characterized by fever, an infection of the gums, progressive and rapid anemia, dyspnea with slight enlargement of the spleen. The leukocytes varied from 7300 to 21,000. Of these the large mononuclear cells formed from 90.6 per cent. to 94.6 per cent., and the polymorphonuclears 2.2 per cent. to 0.1 per cent.

The cells, after being washed three times in 0.85 per cent. NaCl were used for the following experiments. By employing measured quantities of washed cells and heated blood serum, and after five days' incubation at 36.5° C., by determining the amount of digested protein by estimations of the uncoagulable nitrogen content, we have been able to measure the amount of proteolytic digestion. The experiments were all done in duplicate.

1. The leukocytes, after being washed three times in 0.85 per cent. NaCl are made up to a 10 per cent. suspension in 0.85 per cent. NaCl.

	No. of c.c. of $\frac{N}{10}$ NaOH neutralized
10 c.c. of cell suspension + 10 c.c. of heated serum	21.75
10 c.c. of cell suspension + 10 c.c. of heated serum, alkaline	21.65
10 c.c of cell suspension + 10 c.c. of heated serum, acid	5.70
10 c.c. of cell suspension (control)	6.20
10 c.c. of cell suspension heated + 10 c.c. of heated serum (control)	6.92

Digestion took place as may be seen by the table, exclusively in neutral and alkaline media.

At autopsy the lymph nodes were not enlarged. The bone marrow was red and microscopically was composed of cells similar to those seen in the blood during life. Estimations of the proteolytic activity of the marrow showed practically the same result as was obtained with the cells of the blood.

2. Cells of bone marrow treated in serum cells of blood, and made up in a 10 per cent. suspension in 0.85 per cent. NaCl.

	No. of c.c. of $\frac{N}{10}$ NaOH neutralized
5 c.c of 10 per cent. suspension + 10 c.c of heated serum	18.25
5 c.c. of 10 per cent. suspension + 10 c.c. of heated serum, alkaline	16.55
5 c.c. of 10 per cent. suspension + 10 c.c. of heated serum, acid	4.65
5 c.c. of 10 per cent. suspension (control)	2.10
5 c.c. of 10 per cent. suspension boiled + 10 c.c. heated serum (control)	5.3

We next made experiments to see if these cells contained ferments other than leukoprotease. An aqueous extract was made of the cells of the blood, and their lipolytic action tested. Using ethyl

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butyrate as a medium, we found that though the fat splitting was not great, still that a definite lipolytic action could be demonstrated. In this case, then, the large uninuclear cells contained a lipase as well as a leukoprotease.

The marrow cells were only examined for leukoprotease, but this was present in large quantities.

The cells in this case, therefore, contain an enzyme in common with polymorphonuclear leukocytes and granular myelocytes, and an enzyme lipase, which is besides found in the other organs of the body.

Leukoprotease, as far as we know, is either absent or present in exceedingly small quantities in lymph glands under normal conditions, and in the lymph glands from cases of small-celled lymphatic leukemia. The lymph nodes, however, as has been shown by Loevenhart and more recently by Bergel, contain lipase, and since the cells from this case of acute leukemia also contain lipase they possess at least one enzyme in common with lymphocytes and indeed with most tissues of the body. We may, however, conclude that these cells in the acute leukemia are biologically myelocytes, and since they contain an active proteolytic ferment their destruction, which must go on during the progress of the disease, may have some bearing upon the course of the disease. *February*, 9, 1911.

SOME EFFECTS OF UNDERFEEDING ON THE GROWTH OF THE BRAIN.

By Henry H. Donaldson.

(Abstract.)

In following the growth of the brain in the albino rat, I have sought to determine the effects of underfeeding on this organ.

In the experiments to be reported all the rats were killed at the age of fifty days. In those underfed, the underfeeding was begun when the rat was twenty-nine days old and continued for twenty-one days.

At the beginning of the underfeeding the rats weighed 30 to 40 grams and the brain had about two-thirds of its mature weight.

The underfeeding was severe enough to stop body growth and to stop or greatly retard the growth of the brain. The first point examined was the percentage of water in the brain.

Between birth and maturity the percentage of water in the brain falls. At birth it is about 88 per cent., and at maturity about 78 per cent. This fall is an index of a maturing process, and is normally closely correlated with age.

What we find in the brain of the underfed rats is a percentage

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of water characteristic for the age and deviating less than 0.1 per cent. from that in the controls. At the commencement of the experiment, twenty-nine days, the percentage of water was 80.6 per cent. At fifty days the controls gave 79.4; the experimented, 79.3.

In this case then we have succeeded in separating the process of growth from the process of maturing. Underfeeding stops growth, but it does not stop the maturing process, represented by the progressive loss in the percentage of water.

The second matter which I wish to discuss is medullation. From some previous work I had concluded that the medullation process, *i. e.*, the formation of the medullary sheaths, was connected with the normal diminution in the percentage of water characteristic of advancing age. If that relation held in the case of underfed rats, then medullation in the brain of the underfed rats should continue despite the arrest of growth.

According to my observations it does so continue.

I am passing about a series of sections as evidence for this statement.

The explanation goes with the specimens. The middle slide is from an underfed animal which at fifty days weighed 4 grams less than it did at twenty-nine days, and in which the growth of the brain was arrested.

The medullation in the brain is as good as in the controls. The same result was obtained in twelve similar tests.

Here the effect of underfeeding is not easy to explain. Despite the failure of the brain to grow, the myeline has been deposited about the fibers. Thus a compensatory process must have occurred, since it seems probable that unless something else had been removed, the addition of the myeline would have given a marked increase in weight.

It is not the time to discuss this matter in more detail, but if we consider the medullation as a growth phenomenon, then severe underfeeding does not arrest this particular form of growth as we might expect.

I look upon the persistence of both these processes as examples of the very remarkable regulation of nutrition in the central nervous system, a regulation which assures the nerve tissues of nutrition when the other tissues are suffering from a lack of it.

Briefly to summarize results then: Severe underfeeding in the normal albino rat, while it may reduce the body weight below its initial value and greatly retard or even stop growth in the weight of the brain as a whole, does not modify the maturing process represented by the diminution in the percentage of water or the medullation process represented by the formation of myeline about the axones. So long as the animal can live under these conditions, both processes may continue. *February* 9, 1911.

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SPECIMENS PRESENTED MARCH 9, 1911.

DR. J. EARLE ASH:

Cerebral Hemorrhage from Rupture of Aneurysm of Carotid Artery.

Brain from woman, aged sixty-seven years, maniac depressive insanity. Death was sudden. Brain showed blood filling anterior and posterior arachnoid spaces, extending along the Sylvian fissures laterally, longitudinal fissure anteriorly, spinal canal posteriorly. Aneurysm measuring 1 by 1.5 cm. in right carotid artery immediately after its point of entrance into the skull; firmly sclerosed, save for the tip, which was soft, at which point the break occurred. Specimen demonstrates communication between the subarachnoid space and the internal cavities of the brain. Hemorrhage was confined to the subarachnoid space; the tip of aneurysm lying beneath the arachnoid. Clot can be traced from the posterior arachnoid space through the foramen of Majende, Key, and Retzius, into the fourth ventricle, through aqueduct of Sylvius, third ventricle, through left foramen of Monro, into the left lateral ventricle, where it had clotted before it could fill this ventricle or extend into the right (patient found lying on left side). Optic chiasm and tract must have suffered from pressure of aneurysm, but clinical notes are indefinite. One made several years ago speaks of retinal hemorrhages; later notes speak of failing vision. This is the only instance of such condition found in 1360 autopsies performed in State Hospital. Arteriosclerosis in the carotid as it enters the skull is very frequently found, even in the absence of the condition in other arterial systems.

DR. BROOKE M. ANSPACH:

Torsion of a Pyosalpinx.

The specimen consists of a tube and an ovary, removed from a patient who presented the clinical symptoms of appendicitis. The onset was sudden, the pain was more or less confined to the right lower abdomen, and accompanied with rigidity and tenderness. There was fever of 102°, and on pelvic examination a mass could be felt at the brim of the pelvis. There was no history of previous pelvic diseases, and no evidence of specific infection.

Upon making an incision, the appendix was found unaffected. The right tube was purplish blue in color, distended with pus, and twisted upon itself about one and one-half times, the pedicle being formed by the mesosalpinx. The ovary was adherent to the twisted tube.

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The etiology of the condition is somewhat obscure; on the one hand it is hard to believe that a tube in a perfectly healthy condition would undergo torsion, and yet, on the other hand, a pyosalpinx is usually so adherent to surrounding structures that torsion would be impossible.

I am inclined to think that in this case the tube was of an unusual length, was much more convoluted than normal, and had an unusually long mesosalpinx partaking somewhat of the fetal type. There may have been a slight previous infection of the tube, which escaped observation, and its distention may have been secondary to the torsion.

DR. CHARLES C. NORRIS:

Torsion of a Normal Ovary.

Patient, aged nineteen years. Gave history similar to that of acute appendicitis except that no hyperpyrexia was present. No previous attacks. Examination revealed an enlarged, exquisitely tender right ovary. Operation, right salpingo-oöphorectomy. Normal convalescence.

The specimen consists of the right tube and ovary and the vermiform appendix.

Right tube is 8.25 cm. in length. The surface is free of adhesions. The abdominal ostium is open. The inner two-thirds of the organ is small and almost atrophic in size, the diameter at the uterine extremity measuring 3.5 mm., and through the centre of the isthmus 4 mm. At the ampulla the diameter widens out a little more than normally, the greatest width being 7 mm. The walls appear normal in thickness. The lumen is patent and contains a little free blood. The tube is deeply congested, but is much less engorged than the accompanying ovary.

Right ovary is enlarged, but its normal shape is preserved. It measures 6 cm. in its long diameter by 2.10 cm. anteroposteriorly, and 4 cm. in depth. The surface is smooth and free of adhesions. The organ is tense, almost semifluctuant to the touch, and of a deep purplish black color. Its superior portion is somewht drawn out, although its attachment to the broad ligament could hardly be called a pedicle. This portion of the specimen is black. By twisting the ovary from right to left, the original torsion can easily be reproduced. On section, through the capsule, is found to be thin and stretched out. The ovarian tissue is deep purplish black. It is soft, and considerable blood-stained serum follows the knife. A small cyst, filled with a dark blood clot, is present in the inner pole. This has a diameter of 4 mm. With this exception the ovarian substance appears solid. The broad ligament at the point of ovarian attachment is congested.

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Appendix. The vermiform appendix is 6.5 cm. in length and is macroscopically normal.

Histological Description. Right Tube: Section from the isthmus of the tube exhibits engorgement of its bloodvessels, but is otherwise normal. Section through the ampulla shows the peritoneal surface smooth, the muscularis normal in thickness, the mucus folds swollen and blunt. Their ends are free. The investing epithelium consists of a single layer of cylindrical cells which are normal. The stroma of the plica is somewhat infiltrated with free blood. All the bloodvessels of the tube are engorged, and this is especially true of the veins. The lumen is empty. Sections from four different portions of the ovary all present the same general histological character, *i. e.*, normal ovarian tissue densely infiltrated with blood. Indeed, this engorgement was so marked as to obscure the character of the tissue until sections were mounted in which the blood had been previously partially dissolved out. The small cyst noted in the macroscopic description proves to be a Graafian follicle. The bloodvessels are greatly engorged. The capsule is thin and contains free blood. Nothing in the least suggestive of tumor formation is present, the entire picture being that of a normal ovary densely infiltrated with blood and evidently under considerable tension.

Appendix: Sections from the base and tip of the appendix prove the organ normal.

Diagnosis: Torsion of a previously normal ovary; engorgement and secondary involvement of the Fallopian tube; normal vermiform appendix.

A STUDY OF CASE HISTORIES AND AUTOPSY PROTOCOLS WITH SPECIAL REFERENCE TO THE RENAL FINDINGS.

By J. H. Austin, M.D., and O. H. Perry Pepper, M.D.

(Abstract.)

This work was based on an article published in the *Journal of the American Medical Association* for October 15, 1910, by Richard C. Cabot, of Boston, and consisted of the study of 225 case histories, with autopsy records. A comparison was made in each case of the diagnosis justified by careful study of all the data in given case, with the autopsy findings. The effort was made to supplement, or in some cases even correct the recorded diagnosis by all such secondary diagnoses as could be made from any of the clinical data. This was done always in ignorance of the pathological findings. It should in no sense be considered a criticism of inadequacy of the recorded diagnosis, but merely an effort to determine our ability

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to prophecy the details of the pathological findings, in many respects too subordinate to the main condition to be placed in the clinical diagnosis. The cases considered were, for the most part from the medical wards of the University Hospital, and all the cases were autopsied by the Pathological Department of the University of Pennsylvania.

In the cardiovascular system our findings agreed very closely with Cabot's, the chronic valvular conditions being correctly diagnosticated in about 66 per cent. of the cases, while in the acute conditions of endo- and pericarditis only about one-third of the cases were recognized.

Concerning myocardial insufficiency, Cabot points out that the diagnosis of chronic interstitial myocarditis is impossible clinically, and that what we can detect is the evidence of myocardial insufficiency for which various pathological alterations may be responsible. We have, therefore, in our series made simply the diagnosis myocardial insufficiency from our clinical data, but in the study of the autopsy records we have tabulated the various types of myocardial alteration found. In the entire series we have encountered 125 cases of myocardial degeneration, of these we diagnosticated clinically 111, or 89 per cent. In only 4 cases was there clinical evidence of myocardial insufficiency which could not be verified by the autopsy findings. Of these 125 cases, 67 occurred in chronic diseases and the following table will show the relative frequency of the different types of degeneration found:

	Chronic cases,	Cases %	Acute cases.	Cases %
Chronic interstitial myocarditis	40	59	21	42
Fatty degeneration	16	24	6	12
Brown atrophy	9	13	6	12
Fatty infiltration	2	3	1	2
Cloudy swelling	11	16	26	52
Total number of cases	67		50	

In studying arteriosclerosis we found 90 cases, of which 88 were correctly diagnosticated from the clinical data, and in the other 2 cases an error of omission was made. In no case was arteriosclerosis diagnosticated and not found at autopsy. In this connection it is interesting to compare these figures with Cabot's, who found 208 cases of which he correctly diagnosticated only 131, and he made a diagnosis in 12 cases in which the autopsy failed to reveal the condition. It is difficult to explain these errors of commission unless it be assumed that inferential diagnosis was frequently attempted.

In our short series of cases the respiratory system was represented in so few that the figures obtained are of no value.

In our study of nephritis we found 31 cases of acute nephritis, of which 68 per cent. were diagnosticated during life. Some of the

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errors of omission, however, are probably to be explained by the development of the condition only after the patient is obviously approaching a fatal termination, at which time the evidence of a nephritis, even if noted, may readily escape record.

In patients with chronic nephritis we find that the existence of renal disease is quite constantly recognized, but the pathological type of nephritis is frequently erroneously diagnosticated. This is especially true when there is a chronic lesion with a superimposed acute nephritis. Such a double condition is by no means infrequent, having occurred in 37 per cent. of the cases with renal lesions. Chronic interstitial nephritis with superimposed acute nephritis often gives a clinical picture resembling that of chronic parenchymatous nephritis. Also very striking is the fact that the cases which show the most typical symptoms during life are not necessarily the ones that will show the most marked lesions at autopsy, and vice versa.

We conclude, therefore, that although there are two more or less distinct types of chronic nephritis clinically, representing probably two distinct types of functional alteration in the kidney, there are different anatomic lesions that may produce either clinical picture. Therefore, in making the clinical diagnosis of chronic parenchymatous nephritis in a patient who shows edema, pallor, anemia, etc., one should merely use this name in the sense of a designation for the type of symptom-complex and not as a statement of the type of kidney present anatomically. At autopsy one may find chronic parenchymatous nephritis, more rarely chronic interstitial nephritis with superimposed acute cloudy swelling, or occasionally chronic interstitial nephritis alone. Similarly, the clinical designation chronic interstitial nephritis for the symptom-complex that includes high blood-pressure, polyuria, etc., does not necessarily imply the existence of a kidney that we would classify pathologically as chronic interstitial nephritis. That we designate our symptom-complexes by anatomical names is, perhaps, unfortunate, but at present we have apparently no other names to substitute for these.

March 9, 1911.

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